Comments of Mr. P. N. Lee M.A., C.Stat. (Consultant: P.N.Lee Statistics and Computing Ltd)

Part A Chapter 3

Comment 1.

While I am glad that my review on cotinine[1] has been cited (on page V-54), have no objection to being referred to as a consultant with tobacco industry involvement, and have no problems with the conclusions of my work as summarized in the Draft review, I found it odd that the paper is cited as "P.N.Lee, 1999" when all the other references in the Draft do not give initials. A similar citation is made on page V-61 and, amusingly, on page V-78, the reference to my paper appears between Pirkle and Poore and not in its correct alphabetical order.

Response:

Thank you for pointing out this irregularity. ARB and OEHHA staff are currently editing the document to correct these and other typographical anomalies that occur in the draft. ARB has corrected this citation to read Lee, 1999 and has put the reference in the correct order on page V-78.

Part B Chapter 3. Development Toxicity:

I: Perinatal Manifestations

3.2 Fetal growth

Comment 2.

The report considers that there is conclusive evidence of an effect of ETS on fetal growth. I disagree for reasons that are discussed in some detail in the enclosed review[2]. That review includes results from a large number of relevant epidemiological studies. The authors of the Draft chapter may find it useful to check whether, in Tables 1-3, I cite any papers they may have missed.

Response:

The 1997 document found conclusive evidence of an effect of ETS on fetal growth, and this conclusion received general support during the extensive processes of public comment and peer review to which that document was subjected. As discussed in the introduction to the present document, the purpose of this update was not to review or revisit conclusions drawn

in the 1997 document, but to determine whether new evidence that has appeared since that time modifies the conclusion in any way. The conclusion of the present document is that new studies support and strengthen the conclusion reached in 1997 with regard to effects on birth weight.

In order to respond constructively to this comment we have extracted the key points from the review and respond to these individually. The Tables mentioned, and full citations of the sources, are available in the report submitted by Mr. Lee and available on line from his Web site. Citations in the responses refer to papers referenced in the OEHHA (2004) document unless otherwise noted.

Comment 3:

About 60 studies[1-61] have investigated the possible relationship of birthweight to ETS. Smoking by the father has been the most common index of ETS exposure, while other indices that have been used include smoking in the household, smoking at the workplace and the cotinine level of the mother.

Three main endpoints have been used for studying possible effects of ETS exposure on birthweight. One endpoint, used in many of the studies, is the difference in average birthweight between exposed and unexposed mothers. Another endpoint, used in some of the studies, is the risk of having a low birthweight (LBW) infant. This is traditionally defined as less than 2500g.[62] A third endpoint is the risk of having an infant that is "small for gestational age" (SGA).

In view of the known associations between maternal smoking and low birthweight[63] and between maternal and paternal smoking[1,64] most of the studies have restricted attention to nonsmoking mothers. However some studies have based their analyses on all mothers, in most cases making statistical adjustment for smoking.

Response:

Many studies reported separate analyses of non-smoking mothers (Dejmek et al., 2002; Windham et al., 2000; Jaakkola et al., 2001; Ahluwalia et al., 1997) and found elevated risk of low birth weight. Similarly, comparing the intensity of maternal smoke exposure via cotinine measurements with birth outcomes, Kharrazi et al. (2004) found a dose-dependent decrease in BW with increasing cotinine levels. We emphasize these studies in preference to studies that rely on statistical adjustment for maternal prenatal smoking.

Comment 4:

Numerous factors have been linked to low birthweight. These include the sex, parity and gestational age of the child, maternal age, the height and weight of the mother and father, socioeconomic and employment status, and maternal alcohol consumption.[65,66] The ETS/birthweight studies vary widely in the extent to which these factors have been taken into account. While 13 studies[22,27,29,31,40,43,47,48,54,58-61] have adjusted for eight or more factors, some of the studies do not correct for any factors at all. Despite evidence that nutritional factors play a role in birthweight[67] only two ETS/birthweight studies[30,34] have reported taking diet into account as a potential confounder.

Response:

For this reason, we give most weight to the studies that do make adjustments for confounding. We agree that controlling for maternal diet during pregnancy would help clarify the effects of smoke exposure. However, overall, the consistency of the findings argues for causality.

Comment 5:

Of 31 studies relating ETS to the risk of having an LBW infant, four[13,30,33,51] reported a significant ($p<0.05$) increase in risk, one reported a reduction that was marginally significant at this level[5], with the rest reporting no significant association.

Response:

Including studies described in the 1997 document, we present 22 estimates of the risk of LBW associated with ETS. This risk was elevated in the majority of cases with statistical significance attained in five studies, three of which were published since the first document. The absence of statistically significant findings in individual studies is not evidence of the absence of an effect. The association between ETS and LBW was found to be causal in the 1997 document after review by the Scientific Review Panel and the more recent studies support this assessment.

Comment 6:

Of 16 studies relating ETS to the risk of having an SGA infant, four[33,48,49,61] reported significant increases in at least one analysis, and one[40] a significant decrease.

Response:

As noted above, the absence of statistically significant findings in individual studies is not evidence of the absence of an effect. We conclude that the data taken as a whole are suggestive of an association between ETS exposure and small for gestational age.

Comment 7:

Most of the 42 studies looking for differences in birthweight associated with ETS exposure did not report a statistically significant relationship. However 12 studies[9,14,18,20,21,25,33,34,39,43,44,58] have reported a significantly reduced birthweight and one study[16] has reported a significant increase.

Interpretation of the reported associations is made difficult because:

- although increases in risk of LBW or SGA or reductions in birthweight associated with ETS have been reported in four[43,48,58,61] of the 13 studies that adjusted for eight or more potential confounding variables, these were only in isolated analyses for specific endpoints and exposure indices. Most analyses of these four studies showed no significant association. Of the remaining nine such studies eight did not find any significant relationship at all, and one[40] reported a significantly lower risk of SGA associated with ETS exposure.

- some of the studies that have reported significant associations have accounted for no potential confounding variables[9,21,25,33,44,51] or have not restricted attention to nonsmoking mothers.[14,18,48]

Response:

In epidemiology, it is very common to have a number of studies that suggest a risk but do not in themselves reach statistical significance. In the body of evidence for ETS, there are a number of studies of the association between ETS and low birth weight that do reach statistical significance showing a decrement in body weight at birth. The findings of statistically significant elevation in risk of low birth weight associated with maternal ETS exposure, and elevated but not statistically significant risks in several other studies led to the conclusion of a causal association between ETS exposure and low birth weight in our 1997 report. This report was reviewed publicly and by peer review. In addition, studies such as Kharrazi et al (2004) that controlled for a wide range of potential confounders as well as

maternal smoke exposure assessed by serum cotinine levels, found significant ETS effects on several birth outcomes including fetal death, SGA and LBW.

Comment 8:

Some of the ETS/birthweight studies[11,13,16,32,35,37,43,48,52] found that adjustment for potential confounding variables markedly weakened the strength of the reported relationship between ETS and reduced birthweight.

Response:

Since a number of factors may contribute to lower birth weights, it is expected that adjustment for them will reduce the apparent effects of ETS. The important point is that an association between birth weight and ETS remains after adjustment.

Comment 9:

Almost 30 studies have presented data on the relationship between birthweight and extent of ETS exposure. Only five of these[14,20,30,38,39] found a statistically significant trend. In two studies[20,38] the claimed effect is limited to the highest ETS exposure group, data by level of exposure not being shown in two of the other two studies.[14,39] Confounding, and other sources of bias, may contribute to an observed dose-response relationship.

Response:

These studies were published prior to 1997 and so were not reviewed for this update. While confounding may contribute to an association, studies that appropriately adjusted for confounding have found associations that are statistically significant between ETS exposure and low birth weight. This finding was reviewed by the Scientific Review Panel on Toxic Air Contaminants in 1997. Our update strengthens this finding.

Comment 10:

Recent meta-analyses[68] estimate that ETS exposure is, on average, associated with a decrease in birthweight of 25 to 40g. This modest difference, of about an ounce, does not necessarily imply harm to the infant, and can be compared with a recent estimate of 102g for the reduction in birthweight relating to an elevation in altitude of 1000m.[69]

Response:

A recent study by Kharrazi et al (2004) examined birth outcomes in relation to maternal serum cotinine at 15-19 weeks of gestation. Over the range of cotinine values mean birth weight dropped 109 g. Of greater public health consequence was the observation that with higher maternal ETS exposures, a larger proportion of births were shifted to the lower tail of the birth weight distribution curve. There was no ETS exposure level below which birth weight was not reduced. Furthermore, low birth weight is a known risk factor for a number of adverse health outcomes including infant mortality. Thus a reduction in birth weight is considered a deleterious effect. A small reduction in birth weight for a baby that is already small can be serious.

Comment 11:

Reviewers have noted that in some studies the claimed effects of ETS on birthweight are far greater than would seem biologically plausible and are inconsistent with the results of the remaining studies.[70,71] One recent study, for example,[72] estimated, based on results for maternal smoking during pregnancy, that a 1000 ng increase in mean urinary cotinine was associated with a 59g reduction in birthweight, and that ETS exposure at home was associated with only a 21 ng increase in urinary cotinine. These results would suggest a birthweight reduction associated with ETS of about 1g, not the reduction of 50g or more reported in some studies,[9,12,17-21,28,34,43,44,46] many of which are small and take no, or only a few, potential confounding variables into account.

Response:

The more recent studies included in this update generally had better confounder control than the earlier studies cited above and consistently reported decrements in birth weight. The study by Wang et al (1997) mentioned above (as ref 72) reported a birth weight decrement of 57 g for women with urinary cotinine levels of 31-100 ng, which they say is a range found in passively exposed women. This value is similar to the range of birth weight decrements found in both this update and the previous document of 25-50 g. There is not necessarily a linear relationship between dose and birth weight decrement. Many studies have found substantially greater than 59 gm decrements with active smoking as has been well recognized. Overall, OEHHA feels that the data are consistent in finding an association between lowered birth weight and ETS exposure.

Comment 12:

Lack of objective measures of actual ETS exposure during gestation, and reliance on unverified paternal smoking as a measure of exposure, are additional flaws in the existing studies.

Response:

For this reason we give more weight to studies with objective measures of maternal exposure as, for example, the measure of maternal serum cotinine during pregnancy in the study by Kharrazi et al. (2004). It should be noted that exposure misclassification tends to bias towards the null; thus, evidence of an effect is even more striking.

Comment 13:

The evidence, taken as a whole, does not demonstrate that ETS exposure decreases birthweight or increases risk of LBW or SGA.

Response:

We do not agree with this interpretation. We do agree that the evidence for SGA is suggestive. The finding of an association between ETS exposure and LBW has already undergone our public comment and peer review process during the preparation of our 1997 report. The new studies support our previous conclusion.

Part B Chapter 4. Developmental Toxicity:

II. Postnatal Manifestations

Comment 14:

4.1 SIDS

The report considers that there is conclusive evidence of an effect of ETS on SIDS. I disagree for reasons that are discussed in some detail in the enclosed review[3].

Response:

OEHHA staff thanks Mr. Lee for his review, but disagree with his conclusion [and endorse their earlier conclusion (OEHHA 1997) finding an effect of ETS on SIDS], as noted in the following detailed responses.

Comment 15:

There have been a number of recent reviews of the association between SIDS and parental smoking[1,8,20,28]. When attempting to interpret the results relating to ETS exposure it is important to bear in mind the following points:

Some of the studies[10,11,13,25] reporting an association between SIDS and ETS exposure have not adjusted for any other risk factors, while many others[9,12,14,16,17,21,23,26,27] have only taken a few of them into account.

Response:

Consideration of other risk factors is a critical concern, especially in many of the older studies mentioned above. In general, the more recent studies included in this update had better control for confounding and continued to support a causal association.

Comment 16:

Four studies[15,18-20] have taken into account quite an extensive list of potential confounding variables in at least some of their analyses. In two studies[15,20], such adjustment explained about 80% of the increased risk of SIDS associated with maternal smoking after pregnancy, and in a third study[19] it explained about 50%. In the fourth study[18], adjusted results were not reported for maternal smoking after pregnancy, but adjustment markedly reduced the relative risk associated with maternal smoking in pregnancy, from 4.84 to 1.78. Since such adjustments will inevitably be incomplete - partly because not all such factors will have been considered, and partly because data errors or use of surrogate variables limit the ability to control for confounding - it is not implausible that all of the claimed SIDS/ETS association could in fact be explained by confounding.

Response:

Newborns are indeed vulnerable to a variety of environmental conditions that may contribute to SIDS, adjustment for which reduces the apparent risks associated with ETS. However the consistency of the association of SIDS with ETS exposure in a variety of studies after adjustment for multiple confounders reduces the plausibility that the SIDS/ETS association is wholly explainable by confounding. Furthermore, adjustment for all confounders is nearly impossible, and may actually result in over-controlling for confounders masking the ETS effect.

Comment 17:

In a recent study[29], infants with prolongation of the QT interval, as measured by electrocardiograph shortly after birth, had a more than 40-fold increased risk of SIDS. This abnormality, seen in 50% of the infants dying of SIDS, is a major risk factor that could not have been caused by postnatal ETS exposure and which has not been taken account of in any of the epidemiological studies of ETS and SIDS.

Response:

Recent experiments in rats may provide a link between an infant's smoke exposure in utero and prolonged QT interval. Alterations in cardiovascular responsiveness to neurotransmitters were seen in rats after prenatal exposure to nicotine at levels consistent with maternal smoking (Slotkin et al., 1999). This exposure was associated with an increase in cardiac muscarinic type 2 receptors (M2) on which acetylcholine acts to decrease contraction rate. Nicotine exposure has been shown previously to cause a decrease in ß-adrenergic receptors (Navarro et al., 1990) through which heart rate is stimulated. The combination of an increase in inhibitory receptors and a decrease in excitatory receptors would be expected to lead to dis-regulation of heart function, possibly manifesting as an increased QT interval. This study also reported a nicotine-induced reduction in brainstem muscarinic receptors paralleling that seen in infants who have died from SIDS. In these infants there was decreased binding in brainstem areas associated with cardiorespiratory functions (Kinney et al., 1995). Thus ETS exposure may contribute to the risk of SIDS by impairing the ability of the brain and heart to respond appropriately to periods of hypoxia especially in infants exposed to smoke components in utero.

Comment 18:

Even if the association between parental smoking and SIDS cannot fully be explained by uncontrolled confounding by other risk factors, it may result, not from ETS exposure but from an effect of maternal smoking in pregnancy. Some studies have found that the association of SIDS with postnatal maternal smoking or paternal smoking has been reduced[15,16,20] or even eliminated[21] if adjustment is made for maternal smoking in pregnancy or if attention is restricted to nonsmoking mothers, though others have not[14,19].

Response:

Infants whose mothers smoked during pregnancy are indeed at greater risk of dying from SIDS; however, postnatal ETS exposure is an independent risk factor that can exacerbate this effect. Thus a reduction in the apparent SIDS risk after adjustment for maternal prenatal smoking would be expected. Our estimate of SIDS risk for maternal postnatal smoking is from a meta-analysis of studies that controlled for maternal prenatal smoke exposure (Anderson and Cook, 1997). Yet higher risks (OR 3.50) and a dose response were found by Klonoff-Cohen et al (1995) for postnatal ETS from all sources after adjusting for maternal prenatal smoking and other risk factors.

Part B Chapter 6. Respiratory Health Effects

Comment 19:

6.2.1 Asthma induction

My colleagues and I are in the process of conducting an extensive review of the evidence on asthma induction and ETS. Currently, we have data from some 160 studies on our database and hope to analyse it in a month or two. When our conclusions are drawn, I should be able to make the report available.

Response:

OEHHA thanks the commentator for this advance notice and looks forward to seeing the report, although the proposed timetable makes it unlikely that any new materials identified or issues raised therein will appear in the next draft of the OEHHA document.

Part B Chapter 7. Carcinogenic Effects

Comment 20:

I have concentrated my comments on the data for adults, as I have not recently reviewed the data on childhood cancer. In any case, the conclusions reached in the Draft are not very different from those from my 1998 review on childhood cancer[4].

As regards cancer in adults, I have recently reviewed the evidence extensively. The relevant material for lung cancer is described below, while that for other cancers was reviewed in a published paper in 2002,[5] since updated in an unpublished review.[6] Copies of these are enclosed.

Below I present my comments on a site-by-site basis.

Response:

OEHHA thanks the commentator for the review papers supplied. OEHHA staff have read these and taken note of their content, although as explained elsewhere review papers are not automatically noted or abstracted in the OEHHA document.

Comment 21:

7.1 Total cancer risk in adults and ETS

A recent relevant study has been missed.[7]

Response:

OEHHA thanks the commentator for this suggestion. This study (Nishino et al., 2001) is referenced for several site-specific findings, elsewhere in the chapter, and described on page 46 of the draft. The result for all cancers will be added to the revised document.

Comment 22:

7.2 Lung Cancer and ETS

I find it extremely depressing that no mention whatsoever is made of the series of five papers that my colleagues John Fry, Barbara Forey and I published[8-12] in Indoor + Build Environment in reply to the review paper by Hackshaw *et al*[13] in the BMJ. These provide extremely detailed support for our view that the dose-response relationship between lung cancer and ETS exposure may be plausibly explained by (i) bias due to smoking misclassification, (ii) confounding by fruit, vegetables, dietary fat and education, (iii) correction of errors in one published study, (iv) inclusion of results from all pertinent studies and (v) restricting attention to those studies that have adjusted for age. A set of reprints of the five papers is enclosed.

I also feel the report lacks meta-analyses. I enclose up-to-date meta-analyses[14] based on data summarized in another document,[15] also enclosed.

Response:

In spite of the difficulties in accessing the journal cited (it is not indexed in Index Medicus, and in fact covers a very wide range of topics principally of interest to the building industry: we are unsure of the extent of this journal's peer review process in regard to epidemiological

statistics), staff is aware of Mr. Lee's extensive commentaries on the literature relating to environmental tobacco smoke, and have given his analyses due consideration. However, the papers in question were not selected for inclusion in the draft report because we had reviewed them in the public comment period during preparation of the 1997 report.

The draft report is not a de novo analysis of the entire literature on the subject, but rather an update of the OEHHA (1997) report, which treated the subject of lung cancer in particular in considerable depth. OEHHA has not revisited conclusions based on studies reviewed in the earlier document (which have the benefit of peer review both by the Scientific Review Panel for Toxic Air Contaminants and the general scientific community), except where OEHHA was convinced by new data and/or a revised analysis by our staff that a conclusion should be modified. In the case of the papers cited in the comment, the majority of the data included in the analysis predates the 1997 document and was considered therein. Also, many of the arguments are by no means new, and were addressed extensively in OEHHA's 1997 report, and in responses to comments received on the draft of that report. New studies have been included by reference to the primary publications in the scientific literature.

Comment 23:

7.3.1 "Nasal sinus cancer"

The report mistakenly considers cancers of the nasopharynx under this heading. The two cancers should be kept separate. The evidence for nasopharyngeal cancer is highly variable and most unconvincing, as described in my unpublished review of "the epidemiological evidence on environmental tobacco smoke and cancers other than the lung."[6] As is evident from that review, there is another relevant study that has been missed in the draft.[16]

The evidence on nasal sinus cancer is in fact no more than it has been for a number of years. Reasons why the evidence seems inconclusive are given in my review.[6]

Response:

The comment is correct and the text has been changed to reflect the different cancer sites. There are no new studies specifically addressing nasal sinus cancer to alter the conclusion in the 1997 document of an association with ETS exposure. It is of interest to note in a comparison of the risk factors for sinonasal and nasopharyngeal cancers, Zhu et al. (2002)

report that smoking was a risk factor for squamous cell tumors at both sites. It is anticipated that ETS would have similar effects in both sites.

As mentioned in our response to comment 47 by M. LeVois, the results of the Yuan et al. (2000) study suggest a gender difference in cancer susceptibility in which females are more at risk for nasopharyngeal cancer after ETS exposure. For both males and females there is evidence of a dose-response for childhood exposure to both maternal and paternal smoking, although in males the confidence intervals include no effect. The study by Armstrong et al. (2000) did not find an association between nasopharyngeal cancer and ETS exposure in adulthood, but there was a significant association between childhood exposure to parental smoking and subsequent nasopharyngeal cancer (OR 1.54; p = 0.040). This is consistent with the results of Yuan et al. for females and may indicate a developmental window of susceptibility. More recent studies suggest an association between childhood ETS exposure and subsequent development of nasopharyngeal cancer but leave the role of ETS exposure in adulthood undecided.

Comment 24:

7.3.2 Cervix cancer and ETS

Two relevant studies of ETS and cervix cancer have been missed.[7,17] For one of these[17] the title concerns lung cancer but relevant data on cervix cancer are included. See my review[6] for a summary of my views. We agree the data are inconclusive.

Response:

OEHHA thanks the commentator for these suggestions. These studies (Nishino et al., 2001; Jee et al., 1999) are described, and referenced for other site-specific findings, elsewhere in the chapter. The results for cervical cancers will be added to the revised document.

Comment 25:

7.3.3 Bladder cancer and ETS

There is a recent study on this not considered in the Draft.[18] The evidence remains not even suggestive of a relationship.[6]

Response:

OEHHA has added (Zeegers et al., 2002), which is primarily concerned with active smoking, to the revised draft document with regard to both active and passive smoking and bladder cancer. Along with other investigators, these authors found clear evidence of an association between current or former active smoking and bladder cancer: adjusted incidence rate ratios were 3.3 (95% CI 2.4 – 4.6) and 2.1 (95% CI 1.5 – 3.0) for current and former smokers respectively, relative to lifetime nonsmokers. In contrast, exposure to parental smoking or high levels of ETS at work elevated bladder cancer risk, but not significantly (1.2, 95% CI 0.56; 2.4 and 1.4, 95% CI 0.70; 2.6, respectively). There was no evidence of an association between ETS exposure from an ex- or current smoking partner. It is questionable, however, how unexposed the reference population is since the estimate for work exposure compares "high" versus "low" ETS rather than ETS exposure with no exposure. The estimates based on partner smoking status (never, ex, current) do not reflect other potential sources of exposure to ETS. A more complete evaluation of actual ETS exposure is needed to adequately address the question of the role of ETS exposure in bladder cancer.

Comment 26:

7.4.1 Breast cancer and ETS

In view of the report of the Collaborative Group on Hormonal Factors in Breast Cancer[19] that concluded, based on reanalysis of data from 53 studies, that "smoking has little or no independent effect on the risk of developing breast cancer," it would seem extremely unlikely that ETS might cause breast cancer. For reasons discussed in my review,[6] the direct epidemiological evidence that it does so is extremely unconvincing. I regard it as quite amazing that the Draft should reach the conclusion that ETS definitely causes breast cancer.

Response:

As detailed below, and in the revised document, OEHHA disagrees with the assertion in this comment that there is no association between active smoking and breast cancer. The failure of several large studies to reveal such an effect reflects those studies use of referent groups whose lifetime exposure to ETS is uncharacterized, and probably significant. In view of the data suggesting age-dependence of sensitivity, and in particular a higher sensitivity of breast tissue to carcinogenesis during adolescence and prior to the first pregnancy, the use of

spousal smoking habit as a sole, dichotomous measure of ETS exposure seems egregiously inadequate since it largely fails to capture the extent of exposure during the period of greatest sensitivity. The expectation of a strong link between breast cancer and ETS exposure and a correspondingly stronger association with active smoking is valid only if it is assumed that the dose response relationship for tobacco smoke of any type is linear and that mainstream smoke and ETS are equivalent chemically. Although epidemiological studies frequently assume such a dose-response relationship, in this case this assumption is neither necessary, nor supported by the data.

OEHHA has proposed that a) the observed association between ETS exposure and breast cancer is real and causal and b) that the dose-response for the mammary carcinogenic effect of tobacco smoke is non-linear, especially toward the higher dose ranges associated with active smoking. OEHHA sees this as primarily a data-based explanatory hypothesis which succeeds in unifying to a substantial degree all of the observed epidemiological results, without having to resort to any extraordinary deconstruction of the relevant studies. The converse hypothesis, that there is no such carcinogenic effect of tobacco smoke at any dose level, requires detailed, and individually different, dismissals of a substantial number of studies by assuming unproven statistical imbalances, unidentified confounders, and failure of recognized methods for dealing with confounding and covariance. The existence of a mammary carcinogenic effect of tobacco smoke is supported by numerous studies of its individual components, which include several IARC-recognized human carcinogens. Additionally, there are several explanatory hypotheses which can be advanced, with varying degrees of experimental and epidemiological support, for the non-linear dose response relationship. The existence of such plausible mechanistic hypotheses certainly provides support for OEHHA's analysis, but it is not necessary that any or all of these mechanistic hypotheses be proven beyond doubt; the key assumption of causality and non-linear dose response precedes the explanatory hypotheses rather than being derived from them. The pooled analysis by the Collaborative Group on Hormonal Factors in Breast Cancer makes no claims of considering in any way passive smoke exposure. The analysis essentially divided smokers into never versus ever and ex versus current thus providing little information in the way of quantitative exposure to smoke. Under the methods section they state that "no

attention was given to the reported associations of breast cancer with environmental tobacco smoke exposure". If, as we believe to be true, the data supports a relative risk of ETS that is in a range that approximates that of active smoking (for whatever reason) and if most non-smokers have had significant ETS exposure which is certainly the case, particularly in the many older studies included here, then it is not surprising that this analysis would be unable to identify a risk. In effect, the analysis is to a large degree comparing exposed with exposed.

Reynolds et al. (2004) in their recent prospective study (which appeared subsequent to OEHHA's public review draft, but has now been added to the report), did find a significant association between active smoking and breast cancer that increased with increasing duration and intensity of smoking. When the analysis was limited to the 35,123 nondrinkers in this cohort, current smokers continued to have a significantly elevated risk of breast cancer (HR 1.66, 95% C.I. 1.15-2.40). This is in fact a higher HR than the study as a whole and refutes concerns that associations between smoke exposure and breast cancer are actually measuring a surrogate of alcohol exposure.

Comment 27:

I believe that four relevant studies have been missed out.[20-23] Note that when all the relevant data are in, fixed effects meta-analysis shows no association, with a relative risk estimated as 1.06 (95% CI 0.99-1.14). See my review[6] for details.

Response:

Reference 20 (Hirose et al., 1996) is a study of cervical and endometrial cancer, not breast cancer, and is noted as such in the commentator's review paper. Is it perhaps possible that this citation is a cross-tabulation error and the paper Mr. Lee intended to reference is Hirose et al (1995), reference 35 in his review?

Hirose et al (1995) report a Japanese hospital-based case-control study (n = 560) of breast cancer classified according to menopausal status. A significant association between active smoking and breast cancer was suggested by several analyses, including a multivariate analysis considering the various confounding factors. They also found a significant risk for

exposure to ETS, assessed as current spousal smoking status, in postmenopausal women, (OR 1.39, 95% CI 1.04; 1.85), but not for premenopausal women (OR 1.15, 95% CI 0.91; 1.46). Unfortunately, ETS exposure was not subjected to multivariate analysis to control for potential confounding. This study had the advantages of relatively large size and limited potential response bias due to the collection of data prior to disease diagnosis. However, being a hospital-based study limits the ability to generalize the results to the general population. The apparent link between ETS exposure and breast cancer as a function of menopausal status must be interpreted with caution since the analysis was not adjusted for potential confounders, nor did it take into account potential sources of ETS exposure other than spousal smoking. This paper is in the time frame where it would be expected to appear in the OEHHA (1997) review, but is not described there; perhaps there was a delay in access to the original publication. A note of this study will be added to the revised document in relation to active smoking, and referenced with regard to the ETS finding.

Reference 21: (Furberg et al., 2002) has been referred to by Mr. Lee and other commentators, to whom OEHHA is grateful for pointing out this omission. A description and commentary has been added to the document. The paper describes an analysis of data from a population-based case-control study of breast cancer (the Carolina Breast Cancer Study, also the subject of other authors' sub-analyses), which was designed to identify any difference in risk of p53 protein positive vs. negative breast cancer associated with a range of environmental exposures. No such difference was observed for any category of active or passive smoking examined. However, an association was observed for p53-negative breast cancer and long-duration (>20 years) smoking (OR relative to never smokers 1.5, CI 1.1 – 2.1). Small but non-significant elevations in OR for both P53+ and P53- cancers were also noted for former smokers compared to never smokers, but not for current smokers. Smoking status was established by questionnaire: exposure to ETS was identified dichotomously according to whether the respondent currently lived with a smoker. The positive finding with long-term smoking for one category of tumors is an interesting parallel to the recent result reported by Reynolds et al. (2004) and described in the updated document. Other results for associations between tobacco smoke exposures and either type of tumor are non-positive or equivocal, and may reflect partly the inadequate basis for identification of lifetime passive smoking, and

also perhaps the compromises imposed by the prime intent of the study, which was to seek differential impacts on P53+ and P53- tumors. In contrast, Conway et al. (2002) demonstrated that cigarette smoking influences the prevalence and spectrum of p53 mutations in breast tumors. Breast tumors from ever-smokers were more likely to have p53 mutations involving G:C to T:A transversions than non-smokers; current smokers have statistically higher levels of these p53 mutations than non-smokers. These p53 mutations are consistent with exposures to PAHs and nitrosamines which are found in tobacco smoke.

References 22 and 23 are to the published abstracts of posters that were presented at the Annual Meeting of the Society for Epidemiological Research. Unfortunately the level of detail in these brief abstracts is quite sparse, and OEHHA has not been able to identify any subsequent major publications describing these studies. However the results presented are of interest and will be added to the updated report, although they cannot be given the same weight as those described in detail in full papers. OEHHA is grateful to Mr. Lee for drawing our attention to these abstracts.

Rookus et al. (2000) described their analysis of a Dutch population-based case-control study (n = 918) of breast cancer and oral contraceptives, in which lifetime histories of active and passive smoking were collected by interview. Passive smokers were defined as lifetime non-smokers with at least 20 years daily domestic or occupational exposure to ETS, or if someone smoked daily in their bedroom for more than one year. ORs were adjusted for lifetime physical activity level and other potential confounders. When passive smokers were included in the reference group of never smokers, the ORs for current and ex-smokers were 1.0 (95% CI: 0.8-1.3) and 1.3 (95% CI: 1.0-1.6), respectively. When passive smokers were excluded from the reference group, the risk of breast cancer among passive smokers was increased (OR: 1.2, 95% CI: 0.8-1.7). This risk was comparable to the risks of current smokers and ex-smokers relative to non-exposed controls (OR: 1.2, 95% CI:0.8-1.6 and 1.4, 95% CI: 1.0-2.0, respectively). Differential effects of passive exposure before first pregnancy or on P53 over-expression were not detected. This study is of interest in that ETS exposure from both domestic and occupational situations was measured, and directly it

addresses the concern that many studies may miss the effect of active smoking if passive smoking is inadequately measured and controlled for. The authors state:

> "In conclusion: passive smoking seems to slightly increase the risk of breast cancer comparable to the risk increase following active smoking. Therefore, in studies on active smoking and breast cancer risk, the risk estimates will be biased to zero if passive smokers are included in the reference group."

This study is also of interest in that, in common with some others (e.g. Millikan et al., 1998; Manjer et al., 2001; Egan et al., 2002; Furberg et al., 2002) a statistically significant positive result was obtained for ex-smokers even where data for similar groups of current smokers failed to unequivocally demonstrate such an effect. Interpretation of this otherwise unexplained result may be aided by consideration of the hypothesized short-term anti-estrogenic effect of current smoking, and also of the issues of exposure timing during adolescence and young adulthood, which are elaborated in the OEHHA document.

Woo et al. (2000) described a population-based, nested case-control study in Washington County, MD. In 1975, the smoking status of adult household members was determined by census. Incident breast cancer cases (n = 706) during the subsequent 17 years were identified among women census participants through the Washington County Cancer Registry, along with age matched controls (n = 1,426). For all never active smokers, passive smoke exposure was not associated with breast cancer overall (odds ratio (OR)=1.04, 95% confidence interval (CI) 0.83-1.33). This was also true for postmenopausal never smokers (OR = 0.91, 95% CI 0.71-1.18). (Postmenopausal was defined as age >=50 years; it is assumed that this refers to age at diagnosis although the report does not state this explicitly.) However, there was a significantly elevated risk of breast cancer in premenopausal never-smoking women exposed to ETS, relative to those not exposed (OR = 2.78, 95% CI 1.37 – 5.63). Determination of ETS exposure status appears from the limited report to have been on the basis of cohabitation with a smoker at the time of the census. As noted elsewhere, this ignores other ETS exposure situations (e.g. occupational) that are significant for many study populations, and also does not provide information on age or parity at the time of exposure. No efforts to control for confounding factors are described. In spite of these limitations of the study, and its very brief reporting, it clearly shows, as noted by the authors, an association

between ETS exposure and premenopausal breast cancer, although the overall result for all cases (pre- and post-menopausal) is nonpositive. It is not clear from the report whether this difference actually relates to different response according to menopausal status at the time of diagnosis, or whether in fact the key variable is age and/or duration of exposure.

Comment 28:

7.4.2 Stomach cancer and ETS

Two relevant studies have been missed.[17,24] The evidence is not suggestive of a relationship.[6]

Response:

Reference 17 (Jee et al., 1999) is described, and referenced for other site-specific findings, elsewhere in the chapter. The result for stomach cancers will also be noted in the revised document.

Reference 24 (Hirayama, 1984) is extensively discussed in OEHHA (1997). The findings and earlier analysis are briefly referenced in section 7.4.2.1 of the present document. Both OEHHA (1997) and the present document found the evidence for an association between ETS exposure and stomach cancer to be inconclusive.

Comment 29:

7.4.3 Brain cancer in adults and ETS

Two relevant studies have been missed.[25,26] The overall evidence is inconclusive.[6]

Response:

These two reports (Hurley et al., 1996; Blowers et al., 1997) will be noted in the revised document: as the commenter points out, they do not impact the existing conclusion.

Comment 30:

7.4.4 Leukemia in adults and ETS

One relevant study has been missed.[27] It showed no association.

7.4.5 Lymphoma in adults and ETS

One relevant study has been missed.[27] It showed no association.

Response:

Reference 27 (Hirayama, 1987) is a review and meta-analysis of other data reported by this author, which were extensively described and evaluated in OEHHA 1997 based on the original published reports. The present report has concentrated similarly on original reports of studies as opposed to reviews, and also specifically on those publications which have appeared since the publication of OEHHA (1997).

Comment 31:

Other cancers in adults and ETS

As my review[6] demonstrates, there are also some limited data for a range of other cancers.

Response:

OEHHA did not find that any of these results was sufficiently convincing to impact the overall aim of the document, which is to improve and protect public health. However, we appreciate the commentator's review of these data, and will continue to monitor the scientific literature for any further results of interest.

Part B Chapter 8. Cardiovascular health effects

Introduction:

I disagree with the Draft's conclusions about ETS and heart disease for reasons that are discussed briefly in the enclosed unpublished review[28] which is concerned mainly with the epidemiological evidence, and at more length in an earlier published review,[29] which deals with both the experimental and the epidemiological evidence.

As my unpublished review[28] makes clear, there are a number of papers on the epidemiology of ETS and heart disease that appear to have been missed in the Draft. There are four published after 1997 that are relevant.[30-33]

The Draft would improve from having some up-to-date meta-analyses. These are given in an enclosed document.[14]

Comment 32:

As for lung cancer, heart disease studies published in recent years show a weaker relationship of risk to smoking by the spouse than previously published studies. It is notable that the relative risks from the two largest US studies, published in 1995 and 2003, were very close to 1.00 in each sex, and not statistically significant. These studies provide data on a total of over 20,000 heart disease cases, greater than the total number in all the other studies combined.

Response:

The comment does not specify the studies to which it refers, however, the following three studies fit the description of size and publication dates: LeVois and Layard, 1995; Layard, 1995; Enstrom and Kabat, 2003. There were concerns regarding exposure misclassification in both the exposed and control groups in these studies. LeVois and Layard included ex-smoking spouses in the exposed group as though they had smoked for the duration of the study period. In Layard's study, there was substantial difference in age at death between case and control groups, with cases 6-7 years older on average. Since age is a known CHD risk factor, the case and control groups would not have experienced the same age-related risks. The controls might have developed CHD had they lived as long as the cases; this could substantially affect the relative risk estimates. The study by Enstrom & Kabat (2003) based exposure classification on spousal smoking at baseline in 1959. The study fails to control for other ETS exposures at a time when smoking, and hence ETS exposures were more pervasive. In these three studies, the control groups were likely to have contained individuals exposed to ETS thus minimizing the chances of detecting any effect.

Comment 33:

While the overall adjusted relative risk estimates for spousal smoking are statistically significant, they are based on heterogeneous estimates which are substantially higher in small than in large studies. Many of the studies failed to control adequately for confounding or the various other sources of bias present in such epidemiological studies, with none adjusting for misclassification of smoking habits. Heart disease studies show no clearly significant relationship with workplace ETS exposure.

Response:

As regards control for confounding, no epidemiological study is perfect, but the data taken together demonstrate consistency of effect. In the He et al. (1999) meta-analysis described on p. 8-8, the pooled risk estimate from the 10 studies with better control for confounding (1.26; 95% CI 1.16-1.38) was not much different than the risk estimate from all 18 studies indicating that confounding effects were likely minimal.

OEHHA disagrees with the statement on workplace ETS exposure studies. Wells' 1998 meta-analysis of 8 studies of workplace ETS found significant association between exposure and CHD, with higher combined estimates from the studies that had better ETS exposure estimates and better confounding control.

Comment 34:

Again, claims that the epidemiological data for heart disease support an inference of causality[19,20] cannot be convincingly justified.[21]

Response:

The epidemiological data from a number of studies and meta-analyses alone indicate a statistically significant association of workplace and/or home ETS exposure with CHD (see draft Chapter 8). In addition, the inference of causality is supported by studies documenting adverse changes in heart disease-related endpoints after ETS exposure including loss of arterial elasticity (Stefanadis et al., 1998) and function (Otsuka et al., 2001; Raitakari et al., 1999; Sumida et al., 1998). The loss of arterial elasticity following 5 minutes of ETS exposure (as measured by changes in distensibility) was similar to the loss after 5 minutes of active smoking, 21% vs 27% (Stefanadis et al., 1998). Otsuka et al. (2001) reported decreased coronary flow velocity reserve (CFVR) after ETS exposure. In patients with angina, a CFVR of <2 was reported by Chamuleau et al. (2002) to be a significant predictor of coronary events, such as MI and death, in the year following testing. Thus ETS exposure is associated with several negative cardiovascular effects, many of which are also observed with active smoking.

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